CONJUGATION PATHWAYS IN NICOTINE METABOLISM

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The major metabolic pathways in the phase 1 metabolism of nicotine are C-oxidation to cotinine, which in turn is extensively metabolized to *trans*-3´-hydroxycotinine, and the N-oxidation to the two diastereomers of nicotine-N´-oxide. Together with nicotine these major phase 1 metabolites account for about 65 % of the ingested dose.

Glucuronidation is among the most frequently used means by which humans produce polar metabolites of xenobiotics for excretion. Our recent studies have revealed that nicotine, cotinine and *trans*-3´-hydroxycotinine form glucuronic acid conjugates (phase 2 metabolism), which are excreted in the urine.

Characterization of the conjugates, investigation of the conditions for the enzymatic hydrolysis of the glucuronides and an indirect analytical procedure will be presented.

The major phase 1 and phase 2 metabolites of nicotine have been quantified in two studies. In one study, the 24-hours excretion of these metabolites were determined in habitual users of moist snuff, and in the other study the total amount of these metabolites excreted over 94 hours after intravenous infusion of nicotine to a group of abstinent tobacco users were determined.

Our results show that by measuring excretion of nicotine and its major metabolites, 80-90 % of the dose of nicotine could be quantified in human urine.